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RESPONSES TO NITROPRUSSIDE FOLLOWING HEMORRHAGE IN ANESTHETIZED PIGS

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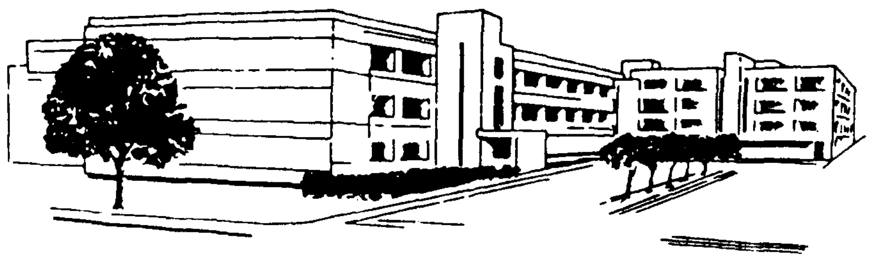

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Responses to Nitroprusside Administration Following Hemorrhage in Anesthetized Pigs. J.D. O'Benar et al.

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The present study was undertaken to examine the physiologic and metabolic effects of pharmacologic vasodilation on recovery from non-lethal severe hemorrhage. It was hypothesized that following hemorrhage a reduction in aortic hydrostatic afterload would lead to a beneficial rise in cardiac output, which would, in turn, improve oxygen delivery. In this study, pigs (n=6 control and n=7 experimental) of body weight 23.5±1.1 kg were subjected to a 40%, 28 ml/kg, arterial hemorrhage while under chloralose-urethane anesthesia. The subjects in the experimental group were then administered nitroprusside at a dose sufficient to maintain mean arterial blood pressure at 50 mm Hg for 60 minutes. Nitroprusside-induced vasodilation significantly lowered systemic vascular resistance, but produced no significant change in the pulmonary vascular bed. Nitroprusside did not produce a significant effect on cardiac output, but did lower oxygen delivery per unit weight. Thus,

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the proposed enhancement of tissue oxygenation resulting from a lowered myocardial afterload did not occur. Venodilation, as a result of nitroprusside administration, may have lowered venous return to the heart and thus blunted the expected rise in cardiac output. As a result of this study, we believe that aggressive vasodilator therapy is an inappropriate treatment following significant systemic hemorrhage.

Key Words: hemorrhage, shock, resuscitation, vasodilator, nitroprusside, cardiac output, swine.

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ABSTRACT

The present study was undertaken to examine the physiologic and metabolic effects of pharmacologic vasodilation on recovery from non-lethal severe hemorrhage. It was hypothesized that following hemorrhage a reduction in aortic hydrostatic afterload would lead to a beneficial rise in cardiac output, which would, in turn, improve oxygen delivery. In this study, pigs (n=6 control and n=7 experimental) of body weight 23.5±1.1 kg were subjected to a 40%, 28 ml/kg, arterial hemorrhage while under chloralose-urethane anesthesia. The subjects in the experimental group were then administered nitroprusside at a dose sufficient to maintain mean arterial blood pressure at 50 mm Hg for 60 minutes. Nitroprusside-induced vasodilation significantly lowered systemic vascular resistance, but produced no significant change in the pulmonary vascular bed. Nitroprusside did not produce a significant effect on cardiac output, but did lower oxygen delivery per unit weight. Thus, the proposed enhancement of tissue oxygenation resulting from a lowered myocardial afterload did not occur. Venodilation, as a result of nitroprusside administration, may have lowered venous return to the heart and thus blunted the expected rise in cardiac output. As a result of this study, we believe that aggressive vasodilator therapy is an inappropriate treatment following significant systemic hemorrhage.

RESPONSES TO NITROPRUSSIDE ADMINISTRATION FOLLOWING HEMORRHAGE IN ANESTHETIZED PIGS -- O'BENAR ET AL.

INTRODUCTION

Hemorrhage impairs the function of the cardiovascular system, posing two immediate problems: 1) loss of transport medium, whole blood; 2) uncompensated decrease in cardiac output. The first problem manifests itself by a decrease in the oxygen-carrying capacity of the circulating blood volume. The second problem impairs the ability of the circulatory system to insure adequate delivery of the remaining blood to the tissues. In the absence of immediate resuscitation with whole blood, the use of any rescue therapy or pharmacologic intervention which protects or restores cardiac output would be a prudent strategy in the treatment of the patient with hemorrhagic hypovolemia. Any therapy which, at the same time, works to prevent further hemorrhage would be ideal.

One of the indirect controls over cardiac output is the "afterload" against which the heart pumps the blood. Physiologically, this afterload is principally the arterial diastolic pressure. When diastolic pressure rises, as it does during recovery from fixed-volume hemorrhage, the afterload also increases. Thus, the hypovolemic heart must do more work to pump out the same stroke volume as it attempts to maintain the remaining cardiac output. In addition, the myocardium, where normal oxygen extraction is high, is extremely prone to hypoxia which may result from a lower circulating volume of red blood cells. Theoretically then, anything which lowers afterload should improve cardiac output, and at the same time reduce myocardial oxygen consumption. With respect to the attenuation of further hemorrhage, simple hemodynamic principles predict a reduction in blood loss from a vascular injury if driving pressure (the intravascular hydrostatic pressure driving blood out of an injury) is lowered. Consequently, when blood loss cannot be controlled by tourniquet or tamponade, reduction of the pressure head forcing blood loss might be a successful temporary expedient, if it could be accomplished without a concomitant loss of vital flow to the heart and brain. During drug-induced hypotension, pressure, rather than cardiac output, is the important determinant of blood loss in patients undergoing surgery (1,2,3). While several hypotensive agents have been used to reduce blood loss in shock (4,5), none have been used to any systematic or extensive degree, probably due to the seemingly paradoxical nature of administering a drug that lowers blood pressure still further. The question therefore remains, can an individual's blood pressure be lowered (by 50% for example) without compromising nutritive flow, if increments in cardiac output and in vasodilation are brought selectively into play?

One drug which might be considered as an appropriate pharmacologic agent to produce hypotensive vasodilation, and at the same time to enhance cardiac output, is sodium nitroprusside. It is thought that nitroprusside's hypotensive mechanism of action is direct relaxation of both arterial and venous vascular smooth muscle (6). The potential benefit for using nitroprusside derives from the fact that hypotensive drugs have found unexpected use in acute situations in the field of neurosurgery. In such cases, nitroprusside is commonly used to promote the maintenance of a "bloodless" or hemostatically controllable operative field (7,8). Furthermore, it is felt that hypotensive therapy can be accomplished without compromising total cerebral blood flow, because cerebral perfusion pressure and cerebrovascular resistance are decreased to a similar degree (9).

While there can be disadvantages to the use of vasodilators, some of those associated with the use of nitroprusside may be offset either by the advantages of its use or by concomitantly administered pharmacotherapy. For example, as patients emerge from nitroprusside medication, hypertensive rebound overshoot can sometimes occur, a complication which purportedly may be controlled or prevented with propranolol (10). Another disadvantage to nitroprusside use is its potential for photodegradation to cyanide before use (11). This can be overcome, however, with the exclusive use of freshly prepared solutions. Degradation of nitroprusside to cyanide in vivo has been reported (12), but this is not felt to be a serious risk when nitroprusside is administered acutely in low doses because it has immediate hemodynamic effects (suggesting rapid metabolism) and it is easily controlled by titration. Finally, a possible drawback to the use of nitroprusside is a drug-induced reduction in renal blood flow, but this is a somewhat unavoidable side effect in any low blood flow state (13).

HYPOTHESIS:

After weighing all of the advantages and disadvantages to the use of vasodilator therapy in hypotensive states in general, and nitroprusside therapy in particular, we formed the following hypothesis: the non-specific nature of nitroprusside in relaxing vascular smooth muscle may prove beneficial in the resuscitation of the hemorrhaged individual. This hypothesis is based upon the following: 1) the lowered cardiac afterload (aortic pressure) should facilitate cardiac output; 2) generalized vasodilation, though lowering perfusion pressure and thus leading to a low blood flow state, may actually promote drainage of otherwise shut-down vascular beds, and thereby enhance the circulating red cell mass; 3) the overall decrease in mean arterial pressure should lower the driving pressure for continued hemorrhage in uncontrolled hemorrhage situations. While unable to test reason #3 in a fixed volume hemorrhage model, we hoped, by our study, to provide evidence supporting reasons #1 and #2.

MATERIALS AND METHODS:

Immature female Yorkshire swine, n=6 control and n=7 experimental, body weight 23.5 ± 1.1 kg (mean$\pm$SEM), were used in this study. Following an overnight fast, an animal was brought to the operating room and administered an intramuscular premedication consisting of ketamine-hydrochloride (2.2 mg/kg), xylazine-hydrochloride (2.2 mg/kg) and atropine (0.08 mg/kg). Then the animal was anesthetized with halothane via face mask, intubated, and maintained with halothane and nitrous oxide during surgery. The animal was then placed in a supine position upon a circulating water blanket to maintain body temperature. An arterial catheter was inserted via the femoral artery and advanced to approximately the level of the diaphragm and connected to a Masterflex peristaltic pump (Cole-Palmer, Chicago, IL) to facilitate blood withdrawal. A second arterial catheter was inserted well into the carotid artery to record blood pressure via a Statham transducer. A Swan Ganz catheter was introduced into the pulmonary artery via the jugular vein using the pressure tracing and the occurrence of wedge pressure as a guide. This catheter was used to record pulmonary artery pressure and central venous pressure, as well as cardiac output by the thermodilution technique using a Gould SP1425 cardiac output computer. The femoral vein was cannulated and connected to a

Harvard syringe pump for nitroprusside or vehicle (control) administration. Temperature was monitored via a rectal probe and recorded.

After instrumentation, the animal was weaned from halothane after intravenous injection of a chloralose (15 mg/kg) and urethane (50 mg/kg) mixture to minimize the hypotensive effect of halothane and to restore a more active baroreflex. Arterial and venous pressures, as well as cardiac output were monitored over this transition period. A twenty-minute stabilization period was then allowed, during which heart rate and arterial pressure remained reasonably constant. At this point baseline readings and blood samples were obtained.

After control readings, the arterial hemorrhage was begun at a fixed rate. The rate was determined by the goal of 40% blood loss (28 ml/kg) over 15 minutes. The blood was removed at a steady (or constant) rate. The Masterflex pump was adjusted slightly to meet this target value. Hemodynamic variables were measured again immediately after blood removal.

Immediately prior to treatment, Sodium Nitroprusside was freshly reconstituted in 5% dextrose and water at a concentration of 200 micrograms/ml. Those animals in the control group received only the dextrose and water vehicle. Both groups received their respective infusions via the femoral vein over a 60 min period. Infusions (either vehicle or nitroprusside) were begun immediately post-hemorrhage. In the vasodilator group, the rate of administration of nitroprusside was carefully adjusted to achieve and maintain a mean arterial pressure of 50 mmHg over the 60 min period. Samples and data were taken at 5 min, 10 min, 20 min, 40 min, and 60 min after commencement of treatment. The average volume of nitroprusside administered was 36 ± 11 ml (mean$\pm$SEM), therefore a like volume and rate of delivery was employed for vehicle administration in the control animals.

After the 60 min treatment period the animals were allowed to recover spontaneously. Samples and data were collected at 10 min, 20 min and 60 min during the post-treatment period. After these data were collected, the animal was euthanized with an overdose of barbiturate.

Cardiac output, blood pressures, arterial plasma lactates and arterial and venous blood gases were measured. In addition, the following variables were calculated:

1. Stroke Volume (SV) (ml/beat) = CO x 1000 (ml/liter)/ HR

2. Systemic Vascular Resistance (SVR) (dyne x sec x cm $^{-5}$) =
   [(MAP - CVP) x 79.98] / CO

3. Pulmonary Vascular Resistance (PVR) (dyne x sec x cm $^{-5}$)
   = (MPAP-PCWP) x 79.98] / CO

4. Left Ventricular Stroke Work (LVSW) (gm x ml/beat) =
   (MAP - PCWP) x SV x 0.0136

5. Right Ventricular Stroke Work (RVSW) (gm x ml/beat) =
   (MPAP - CVP) x SV x 0.0136

6. O_2 Delivery/Weight (ml/dl blood/kg) =
   C_AO_2 x CO x 1O / Wt

7. O_2 Consumption/Weight (ml O_2/min/kg) =
   AVO_2 x CO x 1O / Wt

8. Percent Oxygen Extraction (%) =
   (AVO_2 / C_AO_2) x 100

where CO	= Cardiac Output (liters/min);
HR	= Heart Rate (beats/min);
MAP	= Mean Arterial Pressure (mm Hg);
CVP	= Central Venous Pressure (mm Hg);
MPAP	= Mean Pulmonary Arterial Pressure (mmHg);
PCWP	= Pulmonary Capillary Wedge Pressure (mm Hg);
C_AO_2	= Arterial Oxygen Content (ml/dl blood)
	= (Arterial Hb) x (Arterial % O_2Hb) x (1.39);
C_VO_2	= Venous Oxygen Content (ml/dl blood)
	= (Venous Hb) x (Venous % O_2Hb) x (1.39);
AVO_2	= Arteriovenous O_2 Difference (ml/dl)
	= C_AO_2 - C_VO_2.

The data from the pre-hemorrhage and post-hemorrhage/pre-treatment time points were subjected to a two factor analysis of variance (ANOVA) for group and time effects. The data from the treatment period were subjected to an analysis of covariance with the post-hemorrhage/pre-treatment time point as the covariates. Likewise, the data from the post-treatment period were subjected to an analysis of covariance with the final treatment period time point as the covariates. Statistical significance was assumed when $p<0.05$.

RESULTS:

Pre-hemorrhage/Pre-Treatment Period: The analysis of variance for group and time effects revealed no effects of hemorrhage upon the homogeneity of the population prior to treatment, with one exception. The ANOVA indicated a group difference in oxygen consumption/wt, therefore a Student's t-test was performed. It revealed that at the post-hemorrhage time point, the two groups experienced significantly different oxygen consumptions.

Post-hemorrhage Treatment Period: When subjected to analysis of covariance, the data confirmed the fact that nitroprusside is an efficient, though short-lived, vasodilator. During nitro-prusside infusion, the post-hemorrhage mean arterial pressure (50 mmHg) was significantly lower ($p<0.001$) than that of the control group (Fig. 1). Consequently, the calculated total systemic vascular resistance in the drug-treated group was significantly lower ($p<0.05$) than that of controls throughout the nitroprusside infusion period (Fig. 2). During this same time period, mean arterial pressure for the control group rose steadily, reaching a value of 74 mmHg by the end of the vehicle infusion period.

For all of its power as a vasodilator in the peripheral circulation (i.e., its effects on mean arterial pressure and peripheral vascular resistance), nitroprusside did not have a significant effect in the pulmonary circulation compared to the control animals. There were no significant changes between the groups for pulmonary vascular pressures

(Fig. 3) nor resistances (Fig. 4), indicating an apparent specificity of nitroprusside for systemic arteries and veins.

Treatment with nitroprusside affected tissue oxygenation. The post-hemorrhage increase in oxygen delivery/body weight observed in the control animals was muted during administration of nitroprusside (Fig. 5). This treatment effect, expressed as percent change from the pre-treatment sample, is illustrated in Figure 6). An analysis of covariance indicates that nitroprusside administration resulted in significantly different rates of oxygen delivery/body weight ($p=0.05$). This was coincident with reductions in stroke volume and both left and right ventricular stroke work in nitroprusside-treated swine when compared to the control animals (Fig. 7 & 8). These changes were compensated for by subtle (but not significant) increases in percent oxygen extraction and in oxygen consumption, both of which were greater in the treatment than the control group (Fig. 9 & 10).

Finally, and most importantly, the anticipated augmentation of post-hemorrhage cardiac output by treatment with nitroprusside did not occur. While cardiac output changed over time following hemorrhage, changes in cardiac output were similar for both the control and the treatment groups (Fig. 11).

Post-Treatment Period: During the post-treatment period, values for most measurements in the nitroprusside group returned to or toward control levels (Figs. 1-11). However, the heart rate remained elevated throughout the course of the experiment (Fig. 12), and stroke volume (Fig. 7), as well as left and right ventricular stroke work (Fig. 8) were depressed throughout the post-hemorrhage and post treatment period. In contrast, oxygen consumption/wt (Fig. 10), percent oxygen extraction (Fig. 9) and plasma lactate (Fig. 13) all remained elevated, while total body oxygen delivery returned to a level indistinguishable from the untreated, hemorrhaged control (Fig. 6). The sustained elevation in plasma lactate in the nitroprusside group may indicate a continuing oxygen debt of which the oxygen content, delivery, extraction and consumption parameters, by their elevated values, may indicate a continuing debt to be repaid throughout the course of the post-hemorrhage and post-treatment period.

DISCUSSION:

Immediately following a traumatic vascular injury, it is possible that a depressor agent could be used therapeutically to minimize blood loss. The objective of this study was to investigate whether a lowering of the blood pressure would prove beneficial in maintenance of cardiac output in the aftermath of a life-threatening hemorrhage. Myocardial stroke work is indirectly affected by the "afterload" on the heart: the aortic diastolic blood pressure which the left ventricle must overcome in order to eject its contents. As that afterload increases, the ventricular work required to develop a high enough intraventricular pressure to eject blood from the ventricle must also increase. As a result, myocardial oxygen consumption increases. In the post-hemorrhage period, this myocardial work must be accomplished in the face of a reduced oxygen delivery to the heart (regardless of treatment), as maintenance of cardiac output (i.e., pump function) is the main mechanism available to effect continued tissue oxygen delivery and waste-product removal. Depending upon the magnitude of the hemorrhage, the heart may thus be a compromised tissue on the brink of oblivion, and any therapy which improves myocardial oxygenation or reduces myocardial oxygen demand would be of potential benefit to post-hemorrhage survival.

Several agents have been used in animals and human patients to test the effects of vasodilators during surgery and low blood flow states. In Russia, a tranquilizer called Mebicar was tested for its anti-shock action; its mechanism includes lowering arterial pressure and effects on the "tone of peripheral vessels" (14). In this country and Europe, it has been recognized that although inotropes increase blood pressure and cardiac contractility, they can dangerously increase myocardial oxygen demand (15). So, vasodilator therapy, which can decrease afterload and thereby myocardial oxygen requirements, has been suggested as a possible therapeutic tool in hypotensive crises and for producing hypotensive anesthesia (16).

In the present study, the use of vasodilator therapy following hemorrhage was tested as a means of lowering afterload on the heart, thereby improving cardiac output. While nitroprusside is effective in reducing the cardiac afterload, as evidenced by a 33% decrease in mean arterial and end diastolic pressure (Fig. 1), this vasodilator therapy does not enhance cardiac output (Fig. 11). In contrast to the expected results (i.e., improved cardiodynamic performance and enhanced tissue oxygen delivery), vasodilator therapy had no significant effect on cardiac output and actually depressed tissue oxygen delivery (Figs. 9, 10). In fact, it may well be that the nitroprusside-induced vasodilation caused venodilation as well as resistance vessel relaxation. Were this the case, then venous return would be further compromised -- due to pooling of blood in the periphery -- and cardiac output would decrease due to Frank-Starling mechanisms (i.e., reduced filling of the heart and lowered stretch on myocardial muscle fibers).

CONCLUSION:

In this study, post-hemorrhage nitroprusside therapy was unable to augment cardiac output or tissue oxygen delivery during a time of continued high tissue oxygen demand. As a result of this study, we believe that aggressive vasodilator therapy is an inappropriate treatment following significant systemic hemorrhage.

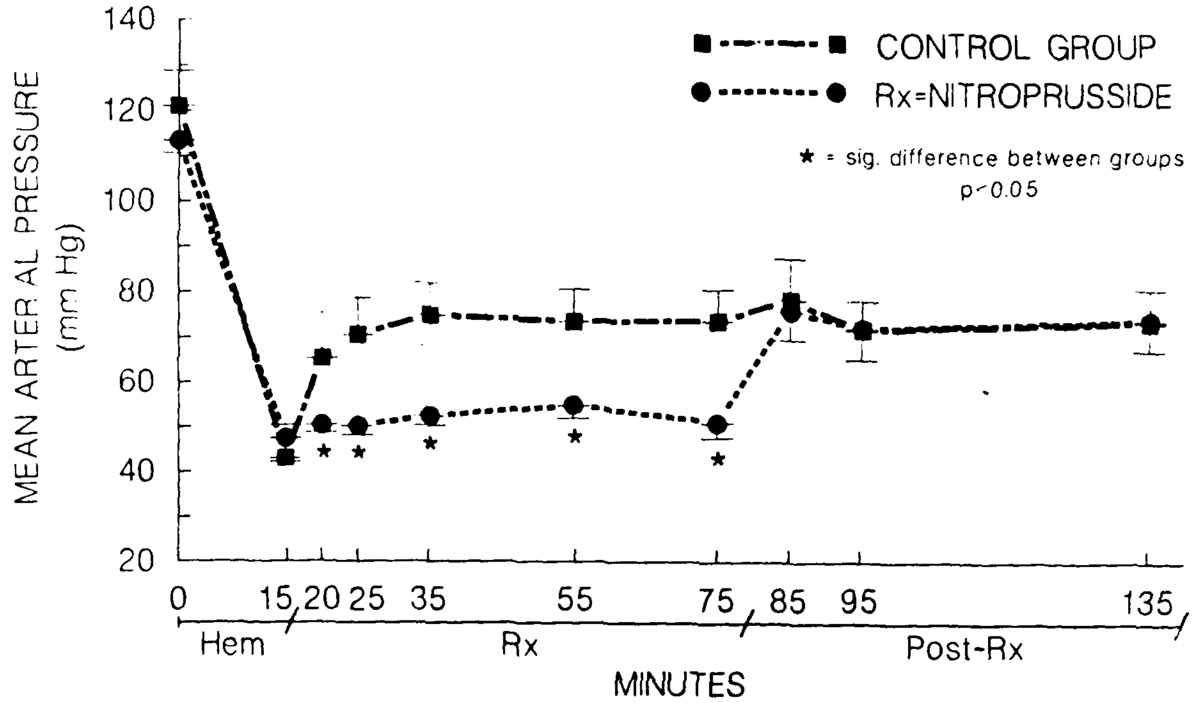
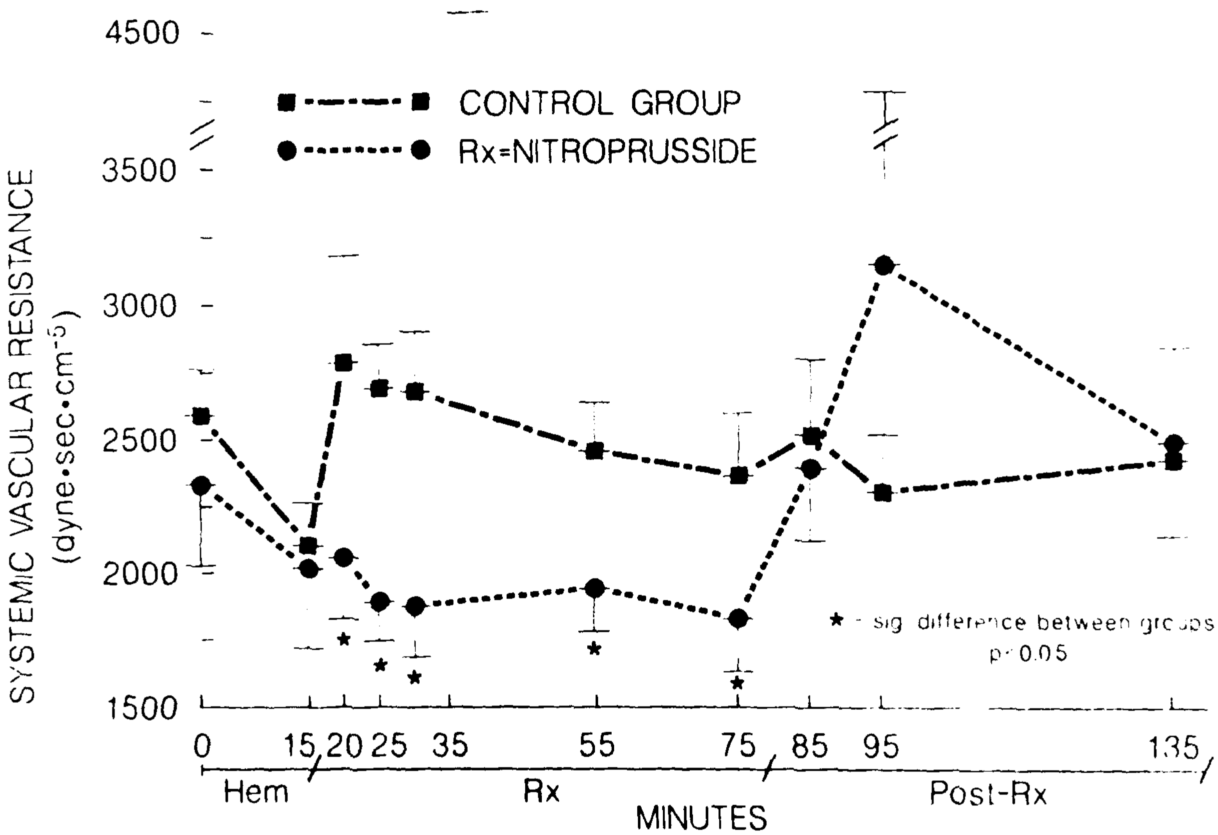


Figure 1. Mean arterial pressure (mmHg) versus time (min). Values are expressed as means±standard error of the mean (SEM).

Figure 2. Systemic vascular resistance (dyne x sec x cm^{-5}) versus time (min).



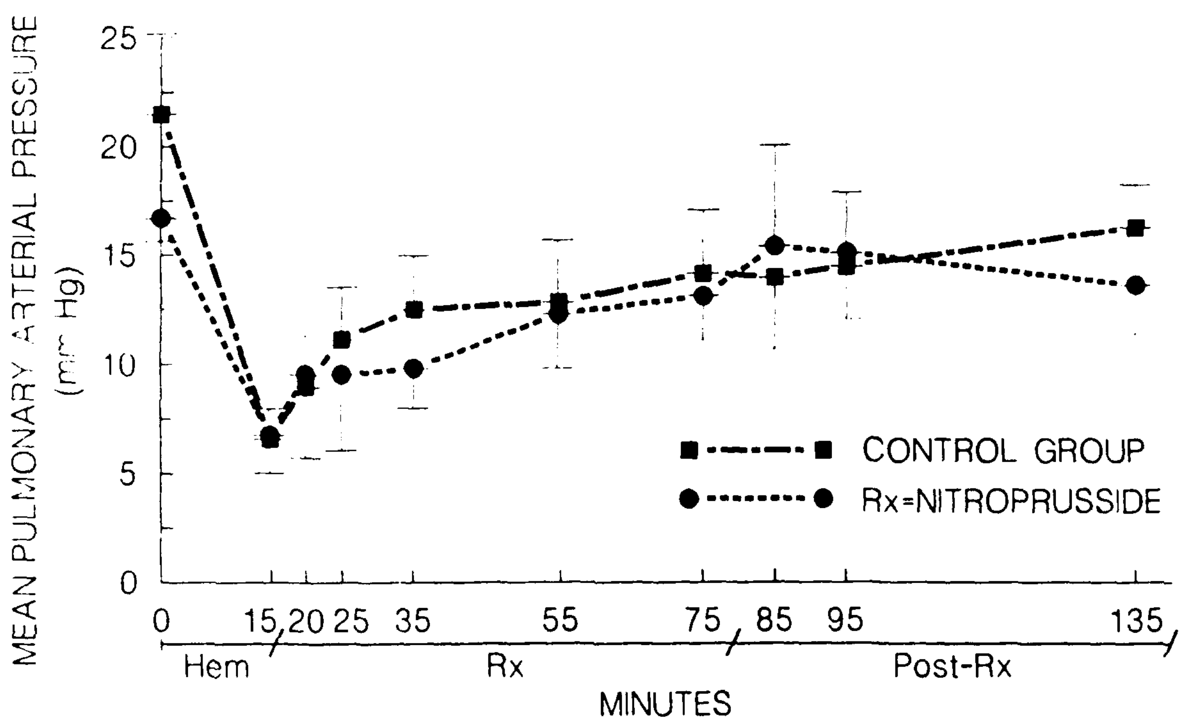
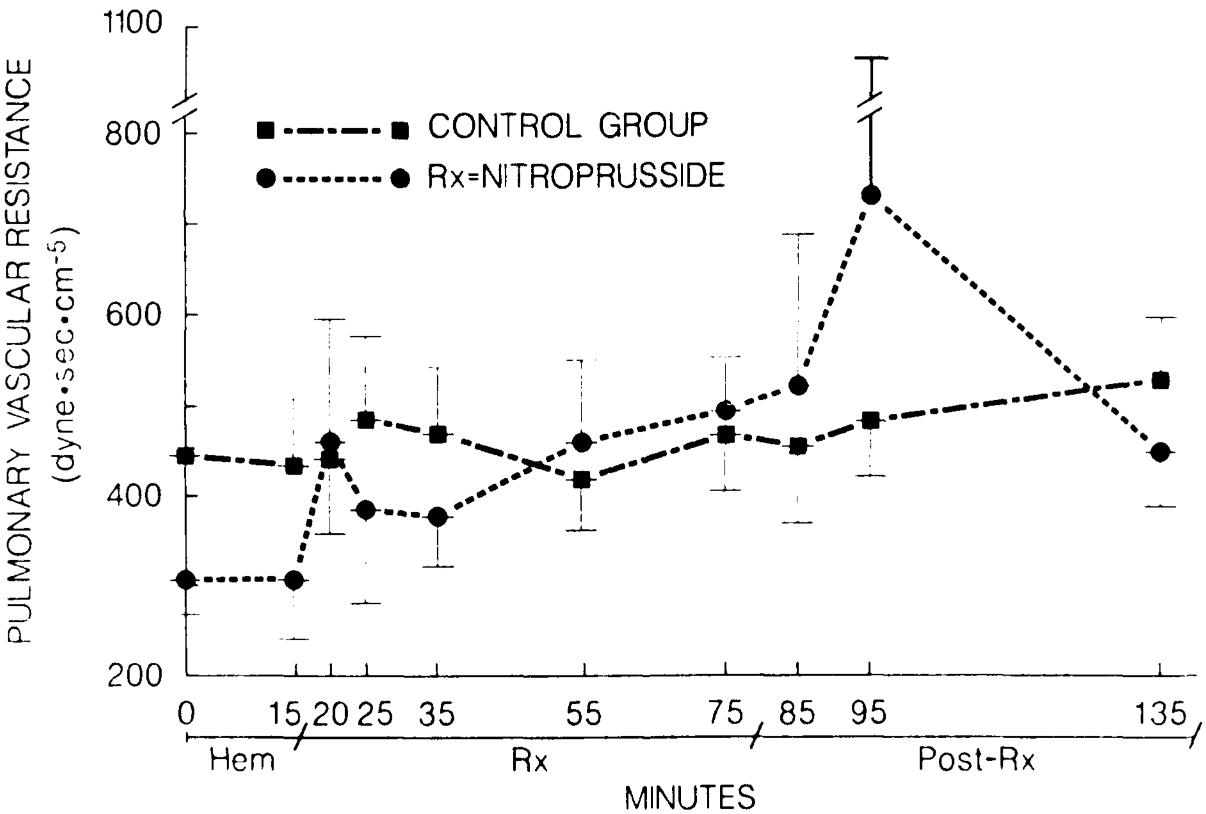


Figure 3. Mean pulmonary arterial pressure (mmHg) versus time (min).

Figure 4. Pulmonary vascular resistance (dyne x sec x cm^{-5}) versus time (min).



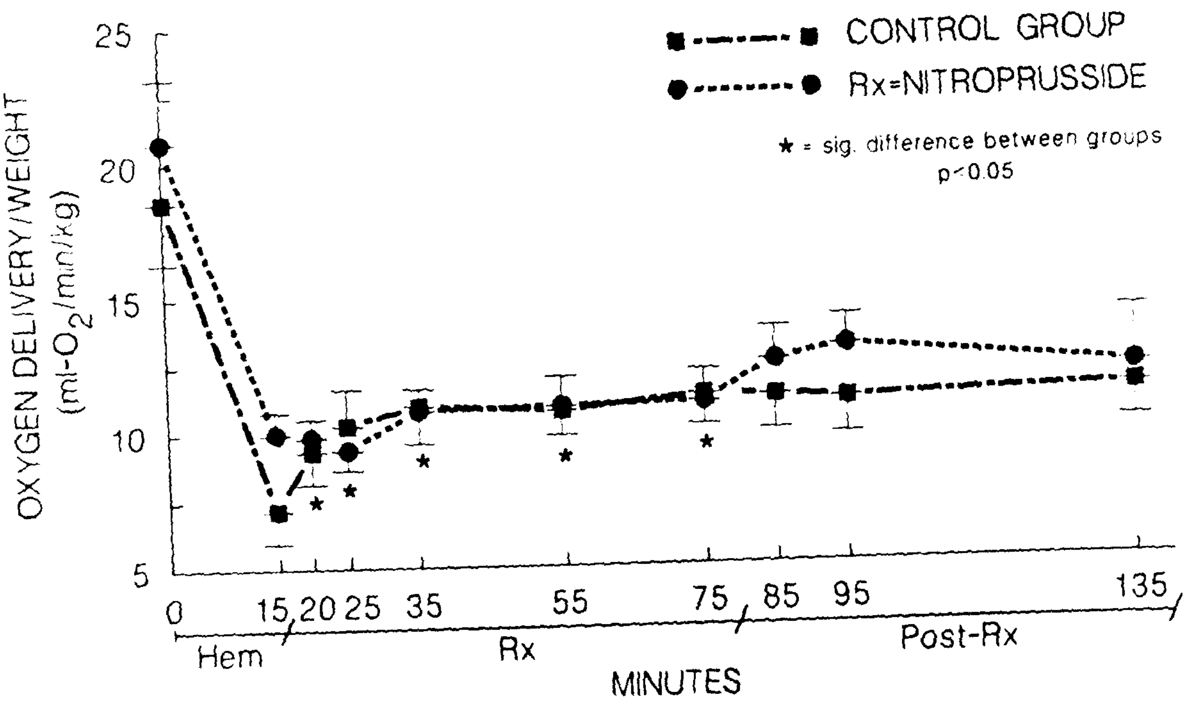
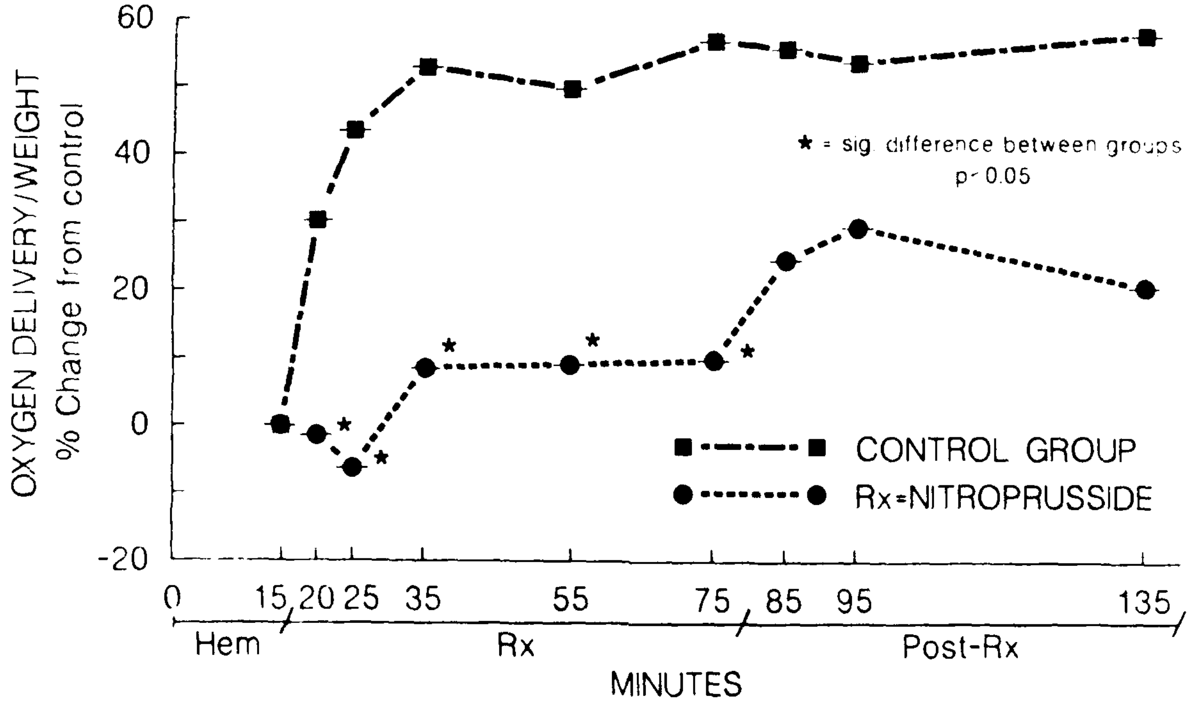


Figure 5. Oxygen Delivery/Weight (ml O_2/min/kg) versus time (min).

Figure 6. Oxygen Delivery/Weight: Percent Change from Control versus time (min).



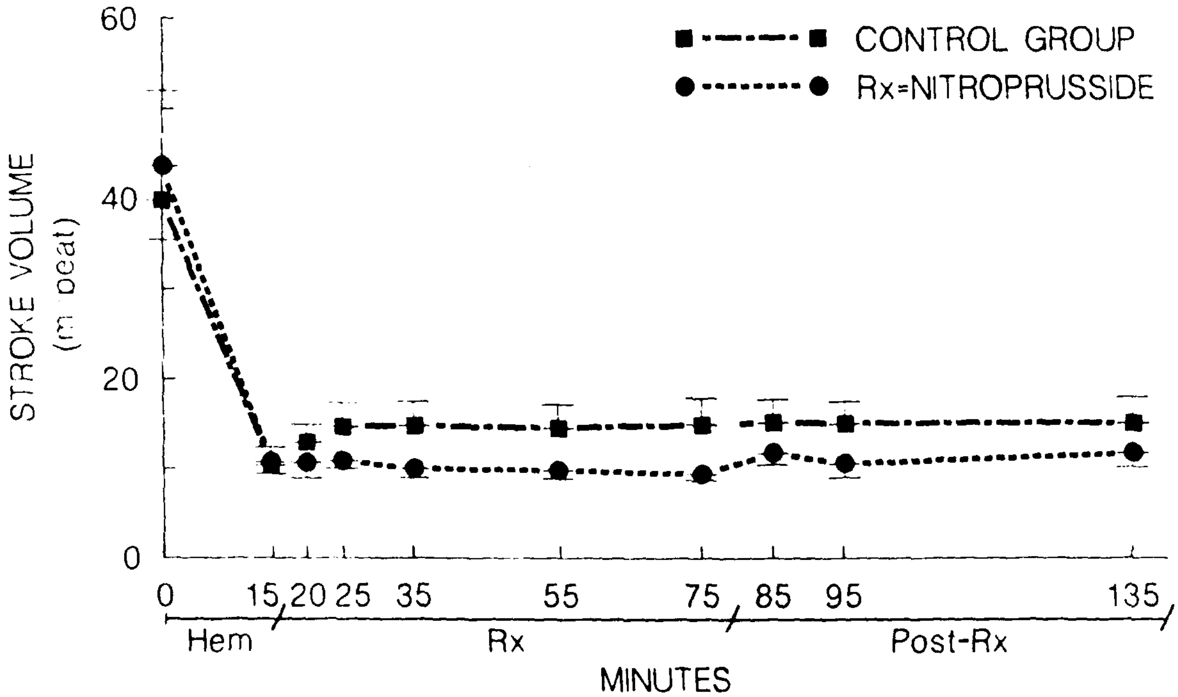
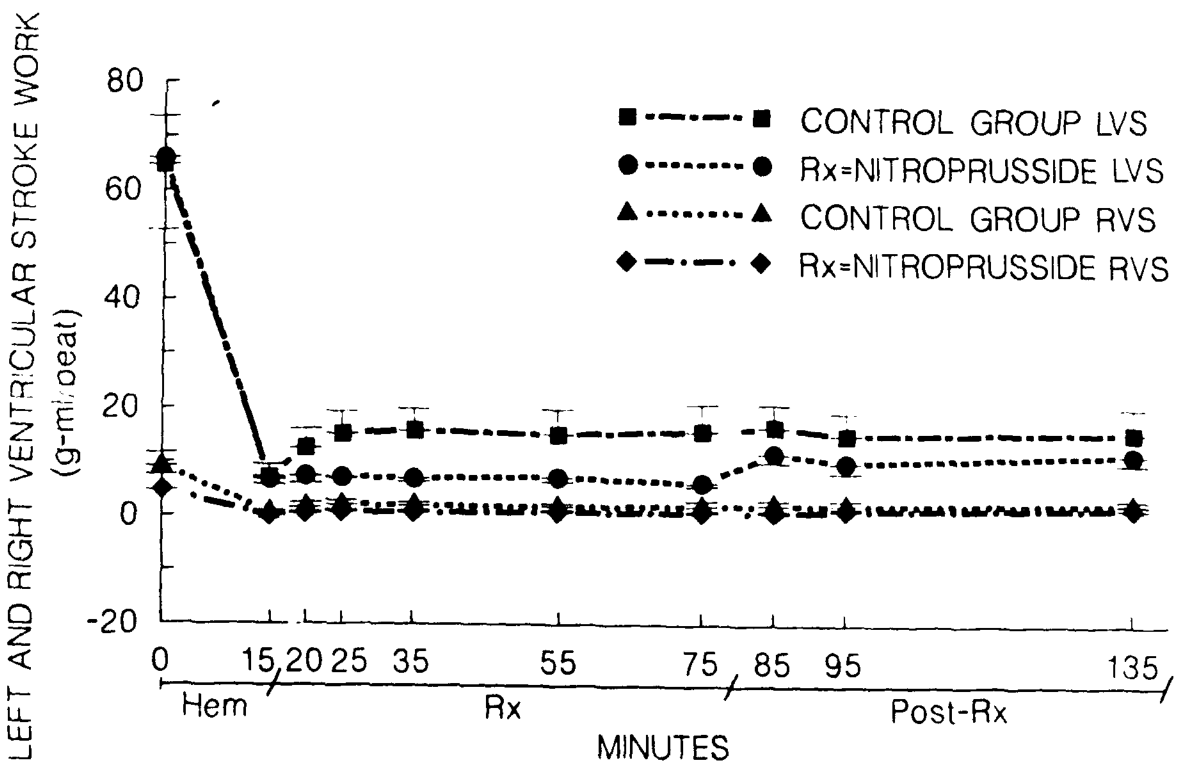


Figure 7. Stroke Volume (ml/beat) versus time (min).

Figure 8. Left and Right Ventricular Stroke Work (gm x ml/beat) versus time (min).



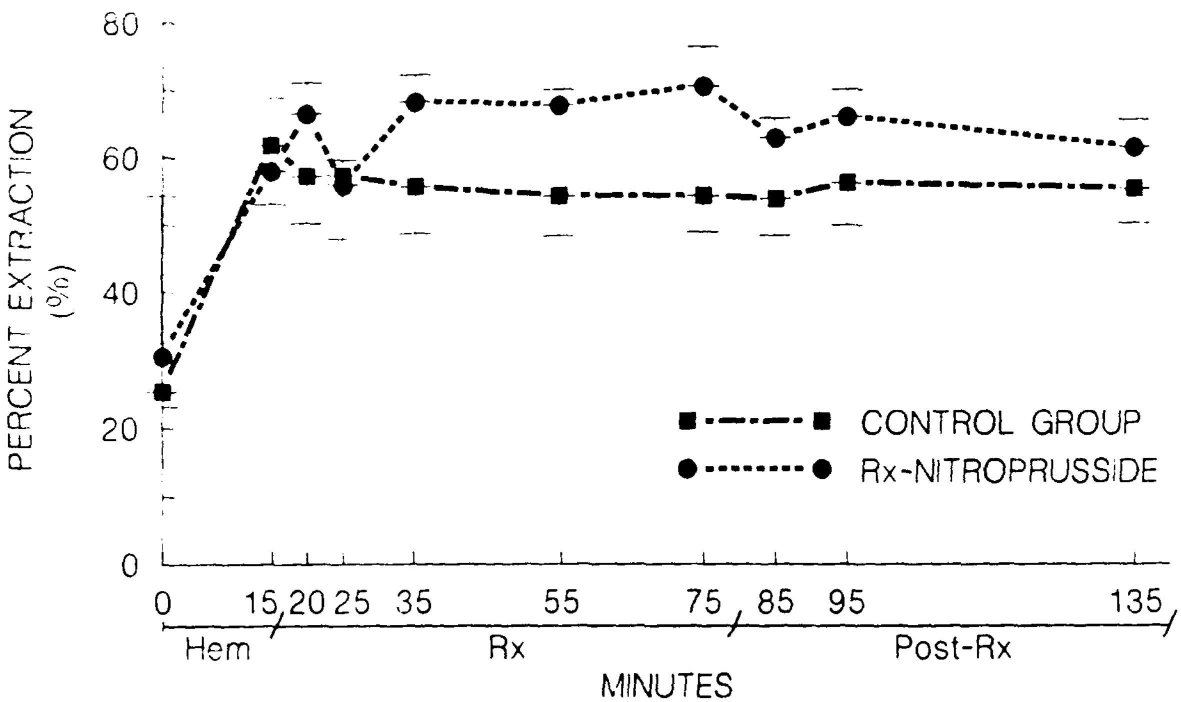
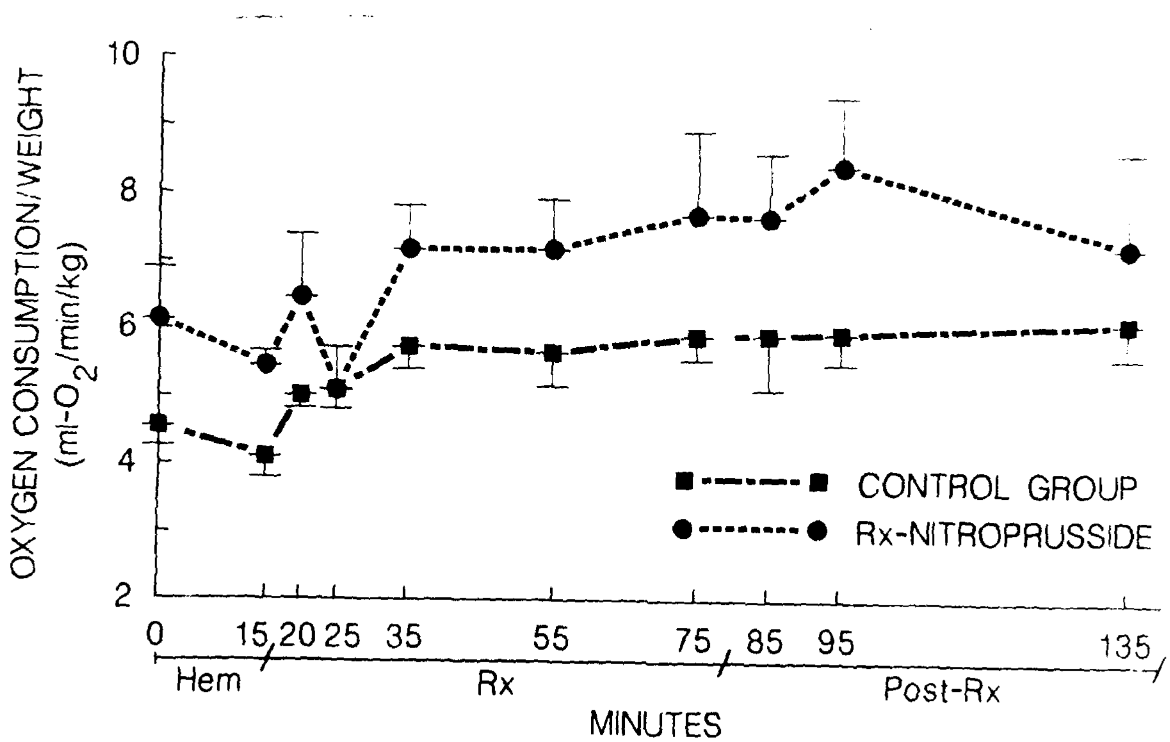


Figure 9. Percent Oxygen Extraction versus time (min).

Figure 10. Oxygen Consumption/Weight (ml O_2/min/kg) versus time (min).



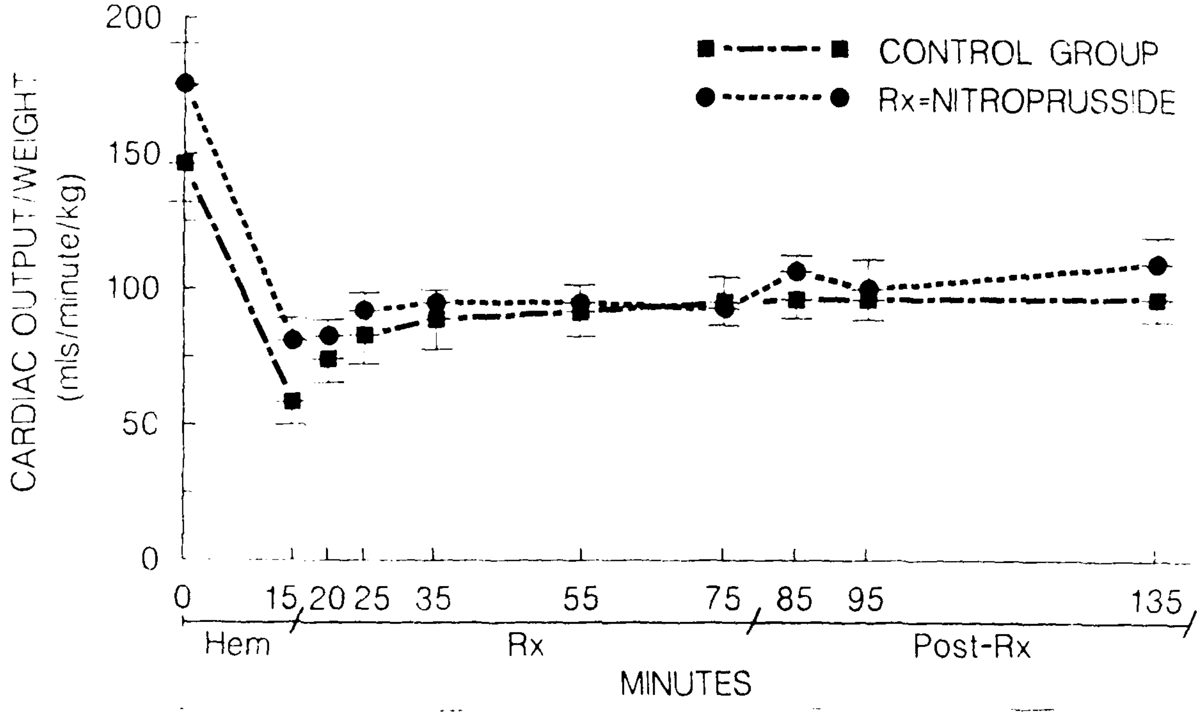
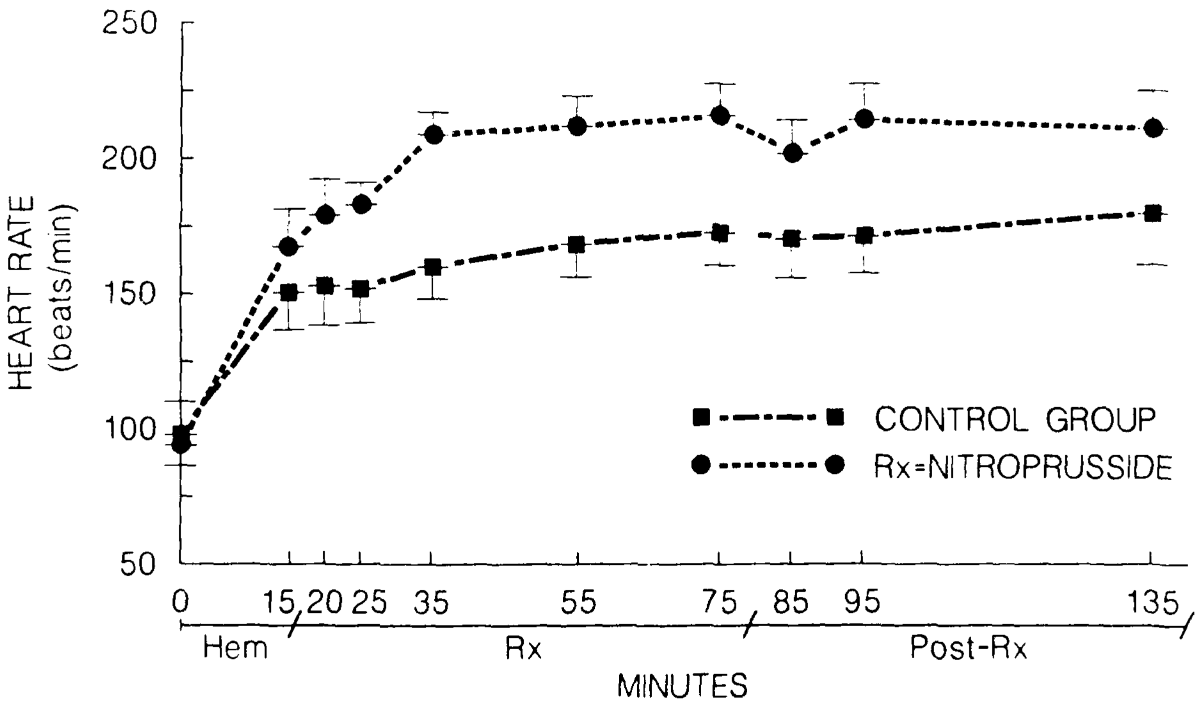


Figure 11. Cardiac Output/Weight (ml/min/kg) versus time (min).

Figure 12. Heart Rate (beats/min) versus time (min).



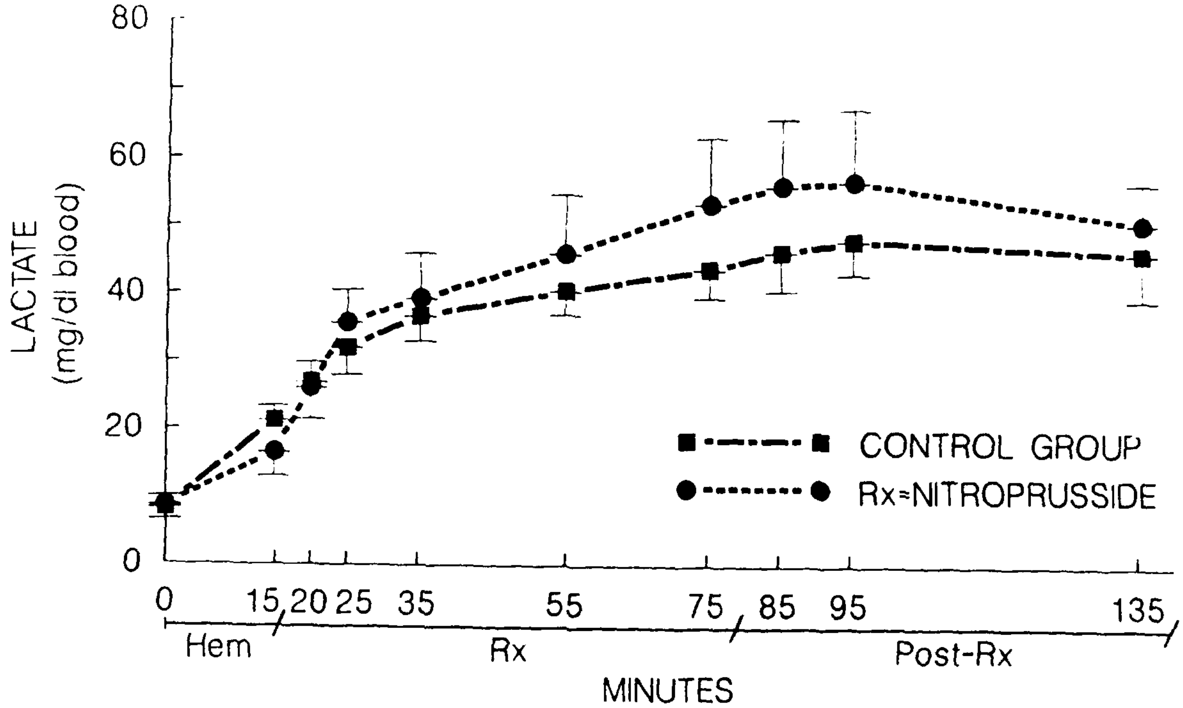


Figure 13. Arterial Plasma Lactate concentration (mg/dl blood) versus time (min).

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